

Assistant Commissioner
for Patents
Washington, D.C. 20231

**AMENDMENT AND REQUEST FOR
RECONSIDERATION UNDER 37 C.F.R. §1.111**

11/B
CD
8/14/02

Dear Sir:

In response to the Official Action (Paper No. 9), dated February 27, 2002, please amend the above-identified patent application as follows:

In the Claims:

Amend claims 1-14, as follows:

- B1
1. (Amended) A method for determining the presence or absence of a target nucleic acid sequence in a sample nucleic acid, the method comprising:
 - (a) exposing the sample to a detection agent comprising a metal surface associated with a SER(R)S active species (SAS) and with a target binding species (TBS),
 - (b) observing the sample/agent mixture using SER(R)S to detect any surface enhancement of the label, wherein the binding of the TBS to the target sequence causes increased surface enhancement of the SAS.
 2. (Amended) The method as claimed in claim 1 wherein the metal surface is not itself effective to cause surface enhancement when present in the detection agent of step (a).

3. (Twice Amended) The method as claimed in claim 1 wherein the detection agent is exposed to the sample in step (a) as two or more separate components.
4. (Twice Amended) The method as claimed in claim 1 wherein the detection agent comprises a first agent and a second agent each having a different TBS, each TBS being effective to bind to the target sequence, and wherein the binding of the first and second TBS to the target sequence brings a metal surface associated with each TBS into proximity thereby causing surface enhancement of an SAS associated with one or both of the metal surfaces.
5. (Twice Amended) The method as claimed in claim 1 wherein the detection agent comprises monodisperse unaggregated colloidal metal particles associated with a TBS comprising a nucleic acid or nucleic acid analog which is complementary to all or part of the target sequence.
6. (Amended) The method as claimed in claim 5 wherein the TBS comprises propargyl amino modified nucleic acid or peptide nucleic acid.
7. (Twice Amended) The method as claimed in claim 5 wherein there are up to 20 TBS per metal colloid particle.

8. (Twice Amended) The method as claimed in claim 1 wherein a surface seeking group (SSG) is used to promote chemisorption of at least one of the SAS and TBS to the metal surface.
9. (Amended) The method as claimed in claim 8 wherein the SSG comprises a triazole group.
10. (Twice Amended) The method as claimed in claim 8 wherein the SSG is modified with a dye which is a SAS.
11. (Amended) The method as claimed in claim 10 wherein the modified SSG is an azobenzotriazole.
12. (Twice Amended) The method as claimed in claim 10 wherein the modified SSG is used to associate the TBS to the metal surface.
13. (Amended) The method as claimed in claim 12 wherein the modified SSG is conjugated to the TBS via a linker group.
14. (Twice Amended) The method as claimed in claim 1 wherein the SAS is present in an amount of up to 100 fold excess over the TBS.
-

A marked-up version of amended claims 1-14 is attached hereto.

Please add new claim 37 as follows:

32 37. (New) The method as claimed in claim 9 wherein said triazole group is the benzotriazole group.

After the claims, please insert the attached ABSTRACT OF THE DISCLOSURE.

REMARKS

The February 27, 2002 Official Action and the reference cited therein has been carefully considered. In view of the amendments presented herewith in the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory period of three months was set forth in the February 27, 2002 Official Action. The initial due date for response, therefore, was May 27, 2002. A petition for a two-month extension of the response period is presented with this Amendment and Request for Reconsideration, which is being filed within the two-month extension period.

Although the February 27, 2002 Official Action did not so state, it is assumed that claims 21-25 and 27-36 have been withdrawn from consideration in this application, in keeping with the lack of unity of invention requirement set forth in the October 11, 2001 Official Action herein. Applicants again note that their election of the subject matter of claims 1-20 for prosecution in this application is without prejudice to their right to file one or more continuing applications, as provided in 35 U.S.C. §120, on the subject matter of all claim held withdrawn from consideration in this application.

The Examiner argues that the lack of unity of invention requirement in this case is proper because claim 1 is unpatentable under 35 U.S.C. §102(b), in view of WO 97/05280. This argument is plainly invalid in that it is based on a false premise, as will be demonstrated herein below. Therefore, in the event that the rejection of claim 1 based on WO 97/05280 is withdrawn, the lack of unity of invention requirement should likewise be withdrawn and claims 21-25 and 27-36 should be examined in the present application.

Turning to the substantive aspects of the March 11, 2002 Official Action, claims 2-14 have been rejected as allegedly indefinite, on several different bases. Specifically, the recitation of "A method...." in claims 2-14 is considered to have insufficient antecedent basis. Claims 2, 4, 7, 9 and 14 are also considered unclear due to the recitations: "capable of" (claims 2 and 4); "more than 1, 2, 3, 4, 5, 10 or 20 TBS per metal

colloid particle (claim 7); "preferably" (claim 9); and "greater than two, 5, 10, 20, 30, 40, 50 or 100 fold excess over the TBS" (claim 14).

Claims 1-6, 8-13 and 15-20 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by WO 97/05280 of Graham et al.

Claims 1-20 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the above-cited WO 97/05280. The Examiner relies on the same disclosures of WO 97/05280 in support of this ground of rejection that were cited in rejecting claims 1-6, 8-13 and 15-20 under §102(b). As for claims 7 and 14, the Examiner concedes that WO 97/05280 does not disclose a method wherein there are more than 1-20 TBS per metal colloid particle and wherein the SAS is present in greater than 20 to 100 fold excess over the TBS. Nevertheless, the Examiner contends that it is *prima facie* obvious to select the specific number of TBS per metal colloid particle and specific concentration ratio of SAS over TBS as a matter of routine optimization with regard to production of desired binding complex, and quantity as well as quality of nucleic acid analyte.

The foregoing objections and rejections constitute all of the grounds set forth in the February 27, 2002 Official Action for refusing the present application.

In accordance with the present amendments, claim 1 has been amended to conform to U.S. practice by changing "characterized in that" to "wherein". Claim 8 has been amended

for the same purpose. In claims 2-14, the introduction of each claim has been changed to read "The method....", instead of "A method....", and thereby establish proper antecedent basis. In claim 2, the recitation of "capable of surface enhancement" has been amended to read "effective to cause surface enhancement". Support for this amendment is provided generally at page 2, line 29 through page 3, line 24, and in more detail at page 11, line 14 through page 13, line 18 of the present specification. It is noted in this connection that the present invention is based on increased surface enhancement in the presence of target nucleic acid sequence. Claim 2, as amended, reflects that the metal surface is not, at the outset, effective to cause surface enhancement. In other embodiments, however, the metal surface may be capable of some surface enhancement, which is increased in the presence of target nucleic acid sequence. Claim 4 has been similarly amended in that recitation "capable of binding" has been amended to recite "effective to bind". The expression "more preferably the benzotriazole group" has been omitted from claim 9. The omitted subject matter is set forth in new claim 37. Claim 7 and 14 have been amended to set forth an upper limit for TBS per metal colloid particle and the excess of SAS over TBS, respectively, according to preferred embodiments of this invention.

No new matter has been introduced into this application by reason of any of the amendments presented herewith. Moreover, none of the present claim amendments is believed to constitute

a surrender of a of the originally-claimed subject matter or a narrowing of the claims in order to establish patentability. The effect of these claim amendments is merely to make express that which was implied in the original wording of the claims.

As a result of the present amendments, it is believed that any indefiniteness that may have been engendered by the claim terminology identified as the bases for the §112, second paragraph, rejection, in Section 2 of the February 27, 2002 Official Action, has been eliminated. Thus, the only matters remaining to be addressed are the anticipation rejection of claims 1-6, 8-13 and 15-20, and the obviousness rejection of claims 1-20, which are each based on WO 97/05280. These last-mentioned two grounds of rejection are respectfully traversed.

Before addressing the above-mentioned prior art rejections, a brief review of Applicants' invention may be helpful to focus on those aspects that are believed to distinguish over the detection method of WO 97/05280.

Applicants have devised a novel SER(R)S based method for detecting or identifying a particular nucleic acid sequence in a sample. Not only does the method of this invention not require amplification of the sample prior to detection, but in preferred formats it can be carried out using simple, one pot, mixing procedures to provide a rapid, highly-sensitive, detection of target sequences, without any requirement to separate unbound labeled targeting agent from labeled target complexes. This is achieved by making the functionality of the SER(R)S surface

dependent on the presence of the target sample. Thus, unlike certain existing techniques that employ labeled probes, unbound labeled target will not generate a false result if present during detection.

In known nucleic acid detection formats, such as those described in WO 97/05280 which is cited by the Examiner as evidence of unpatentability in this case, metal colloid which has been carefully aggregated in a controlled manner is added to labeled target complex prior to detection. In the present invention by contrast, the aggregation of colloidal SER(R)S surface is actually dependent on the presence of target sequence, with the attendant advantages described above. Thus, the method of this invention is characterized in that it is the binding of the TBS to the target sequence which itself causes surface enhancement of the SAS.

Another notable difference between applicants' method and those in the art is that the metal surface, in the form in which it is present in the added agent, is not itself effective to cause surface enhancement. Thus any unbound detection agent present in the system following exposure of the sample to the agent need not be removed prior to the observation step. Accordingly, given that the detection agent will generally be present at great excess over the target material, unbound agent will be present in the system during detection, but owing to the nature of the method, will not interfere with the results. The method is therefore a true "one pot" detection system.

The result of the observation is correlated with the presence or absence of the target sequence, optionally by comparison with reference data.

The method of this invention is particularly susceptible to giving rapid information about whether a known, or at least predetermined, target sequence occurs in a sample nucleic acid.

Because WO 97/05280 neither teaches nor suggests the essential aspects of Applicants' nucleic acid sequence identification method and its attendant advantages, as briefly outlined above, the cited reference fails to provide a proper factual basis for rejecting Applicants' claims, as the following discussion will clearly demonstrate.

A. WO 97/05280 Fails to Anticipate the Subject Matter of Claims 1-6, 8-13 and 15-20

Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the allegedly anticipatory reference. In re Arkley, U.S.P.Q. 524 (C.C.P.A. 1972). Applying this rule of law to the present case, the 35 U.S.C. §102(b) rejection of claims 1-6, 8-13 and 15-20 is plainly improper, because the subject matter of the rejected claims is nowhere identically disclosed or described in WO 97/05280.

The present invention and its relationship to the published art are discussed generally in the present specification at page 5, line 31 through page 8, line 15.

Figures 3(a) (i) and (ii) schematically illustrate one particular embodiment. Referring to this Figure, a detection agent comprising a SER(R)S active species and a target binding species (generally nucleic acid, which binds sequence X') is already bound to a metal particle (e.g. via a surface seeking group). However this agent is not readily detectable because the metal particle, being non-aggregated, is not effective to cause surface enhancement of Raman spectroscopy. A further detection agent of similar composition binds sequence Y'.

In the presence of target sequence X'-Y' the agents bind adjacent to one another and this causes the metal particles to come together, thereby causing surface enhancement of the active species. Thus, the only agents detected will be those bound to the target. If the target sequence is not present there will be no binding of the aforementioned detection agents, and, consequently, no increased surface enhancement of the SAS.

By contrast, the nucleic acid detection method of WO 97/05280 is substantially different from the method claimed by applicants herein, and embodies an earlier, more basic, detection concept. A proper appreciation of the detection method of WO 97/05280 can be facilitated by reference to the schematic diagram attached as Exhibit A, which illustrates the method.

In (i) of Exhibit A, a detection agent comprising a SER(R)S active species is bound to target binding species (generally nucleic acid, which binds sequence X'). In preferred embodiments, it may also include a surface-seeking group capable

of binding to a metal surface. However this is not readily detectable because it comprises no metal surface at all to cause enhancement.

In (ii) of Exhibit A, in the presence of target sequence X' the agent binds to the target sequence. Of course, this does not cause surface enhancement of the active species, because there is still no metal surface present.

At this point in the method of WO 97/05280, any SER(R)S active species present can be detected, even at very low concentrations, by addition of a metal surface capable of surface enhancement e.g. preaggregated colloid, i.e. (iii). If this is preceded by a washing step, then only the detection agent bound to target will be detected.

Thus, it can be seen that in terms of components (i.e. use of a non-aggregated metal particle), steps of operation (i.e. what is mixed with what prior to detection), and effect (the present invention is a '1 pot' detection system in which everything can be added together), the applicants' invention is quite distinct from WO 97/05280.

Addressing some of the specific points made by the Examiner in turn:

Concerning claim 1 (page 4 of the Official Action) WO 97/05280 (claim 1 and Figure 3-20) does not teach binding of the TBS to the target sequence actually causing increased surface enhancement of the SAS. SER(R)S active surface of WO 97/05280 claim 1 is simply added to the detection sample.

Concerning claim 2 (page 4 of the Official Action) WO 97/05280 (at page 23) does not teach the actual use of a metal surface that is not itself effective to cause surface enhancement. Indeed, the cited passage explicitly requires the contrary.

Concerning claim 4 (page 4-5 of the Official Action) WO 97/05280 (at Table and pages cited by Examiner) does not teach separate agents which have the property of bringing respective metal surfaces into proximity.

Concerning claim 5 (page 5 of the Official Action) WO 97/05280 (at Table and pages cited by Examiner) does not teach monodisperse, unaggregated colloidal metal particles. For example, page 24 cited by the Examiner teaches that where colloidal metal particles are being used, they are aggregated prior to use (see line 14).

Nor do applicants accept that the other claimed features are disclosed as asserted by the Examiner, but this is nevertheless moot since all claims depend directly from, or incorporate the features of, claim 1.

In view of the substantial differences between Applicants' nucleic acid identification method and the detection method disclosed in WO 97/05280, the §102(b) rejection of claims 1-6, 8-13 and 15-20 based on WO 97/05280 is untenable and should be withdrawn.

B. The Subject Matter of Claims 1-20 is not Rendered
Obvious by the Disclosure of WO 97/05280

Applicants respectfully submit that WO 97/05280 fails to establish that the subject matter of claims 1-20 is *prima facie* obvious.

Claims 1-6, 8-13 and 15-20 are clearly patentably distinguishable from WO 97/05280 for the reasons states above with respect to the §102(b) rejection. Moreover, the disclosure of WO 97/05280 fails to provide the motivation or incentive to make the substantial changes to the nucleic acid detection method described therein required to arrive at applicants' invention.

As for claims 7 and 14, these are dependent claims that depend indirectly or directly from claim 1, and, as such, must be interpreted to include all of the features of claim 1. It necessary follows, therefore, that claims 7 and 14 are non-obviousness because the claims from which they depend are non-obvious. In re Fine, 5 U.S.P.Q.2d. 1596 (Fed. Cir. 1988).

In view of the present amendments and the foregoing remarks, it is respectfully urged that the rejections set forth in the February 27, 2002 Official Action be withdrawn and that this application be passed to issue, and such action is earnestly solicited.

Respectfully submitted,

DANN DORFMAN HERRELL &
SKILLMAN, P.C.

By:



Patrick J. Hagan
Registration No. 27,643

PJH:ksk